APPENDIX 2: SUMMARY OF THE LITERATURE

CLOZARIL® (clozapine) and SUICIDIAL BEHAVIOR

Document type:	Advisory Committee Briefing Document – Appendix 2
Document status:	Final
Release date:	October 1, 2002
Number of pages:	15

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

Search Strategies

The *Medline* (1966 to date), *Biosis* (1993 to date), *Embase* (1974 to date), *Psycinfo* (1887 to 03 October 2001), *Derwent Drug File* (1983 to 2001), and *Sandoz Medical Document* (1966 to date) databases were searched using the following searches: clozapine/Clozaril® /Leponex® and suicide. After review of the content of these searches, 58 articles were requested, obtained, and reviewed. In addition, an independent internet search was performed using Pubmed, a service of the National Library of Medicine, using the search terms clozapine and suicide and clozaril and suicide. From this search, an additional four papers were identified, requested, obtained, and reviewed. In reviewing all of the publications obtained, an additional eight papers, which were identified from the reference lists of these publications, were obtained and reviewed for relevance. In summary, 70 articles were obtained and reviewed. Of these 70 articles, 34 were considered to be pertinent to this submission.

Of 34 publications pertinent to the effects of Clozaril on suicidality, none were double-blind. They were categorized as population studies (6), non-population studies (5), case reports/observational data (6), and review articles (17) and summarized in Table 1 and in the narrative below.

POPULATION STUDIES

1. Walker AM, Lanza LL, Arellana A, et al. Mortality in current and former users of clozapine. Epidemiology 8; 1997: 671-677.

Summarizing a comprehensive, retrospective review of clozapine's effect on mortality, Walker et al compared rates of various causes of death in 67,072 current and former clozapine users in the United States from 1991 to the end of 1993. This study linked data from the National Registry of Clozapine Recipients to the National Death Index and Social Security Administration Death Master Files. To reduce the number of patients in the cohort whose indication was Parkinson's disease rather than schizophrenia, a detailed analysis concentrated on the age range from 10 through 54 years. Effects of current, recent, and past clozapine exposure on mortality in this population of schizophrenics were compared. During the 3-year study period there were 396 deaths in this age group. Almost one-third of the deaths were from external causes, including suicides, accidents and homicides. Suicide accounted for 19% of all deaths. Relative to the incidence of suicide during past clozapine use, there was a substantial deficit of suicides during the period of current clozapine exposure. The rate ratio of suicide in current clozapine users compared with past exposure was 0.17 (95% CI: 0.10-0.30). The authors concluded that clozapine treatment appears to reduce mortality in severe schizophrenics, mostly by decreasing suicide rates.

2. Reid WH, Mason M, Hogan T. Suicide prevention effects associated with clozapine therapy in schizophrenia and schizoaffective disorder. Psychiatric Services 1998;49: 1029-1033.

This retrospective study examined annual suicide rates over a 2-year period (1993-1995) among an annual average of 30,130 patients with schizophrenia and schizoaffective disorder who had received services from the Texas Department of Mental Health and Mental Retardation. Eighty-six percent (86%) of the patients were between the ages of 18 and 59, and 13% were 60 years of age or older. Suicide rates among a subgroup of 1,367 patients treated with clozapine were evaluated over a 6-year period (1991-1996). Patients included in this cohort had been receiving clozapine for at least 30 days and had not discontinued the drug for more than 14 days. Patients for whom clozapine had been prescribed, but for whom no information about the duration of treatment or drug discontinuation was available, were also included. Only one suicide occurred in this subgroup of clozapine-treated patients during the 6-year study period. Given an average of 1,310 patients continuously receiving clozapine each year, the annual suicide rate for clozapine-treated patients was 12.74 per 100,000, substantially lower than the rate of 63.1 patients per 100,000 calculated for the average annual total study population of 30,130 schizophrenic and schizoaffective patients. This study suggests that clozapine therapy was associated with a lower suicide rate compared with therapy with other antipsychotic drugs.

3. Munro J, O'Sullivan D, Andrews C, Arana A, Mortimer A, Kerwin R. Active monitoring of 12,760 clozapine recipients in the UK and Ireland. Br J Psychiatry 1999;175:576-580.

To quantify the risk factors for agranulocytosis in treatment-resistant schizophrenics receiving clozapine treatment, a retrospective analysis was performed using data from 12,760 subjects in the UK and Ireland. These data were collected by the Clozapine Patient Monitoring Service [CPMS] for the period from January 1990 to April 1997. The duration of clozapine treatment ranged from 1 day to 7.6 years, with a mean dose (after 12 weeks of treatment) of 388 mg/day (mean maximum dose of 462 mg/day). Results of the analysis showed that the cumulative incidence of agranulocytosis was only 0.73%, and this condition was reversible in all but two cases. Only 13 deaths were confirmed suicides. Literature on suicide and schizophrenia were reviewed. Studies presenting the expected number of suicides in the national population were compared with the suicides in the UK cohort. This cohort of clozapine-treated patients experienced a suicide risk one-fourth the rate expected for schizophrenics in the general population. The authors acknowledged growing evidence of an anti-suicidal effect of clozapine.

4. Sajatovic M, Bingham R, Garver D, et al. An assessment of clinical practice of clozapine therapy for veterans. Psychiatric Services 2000;51:669-671.

This retrospective study analyzed treatment outcomes of schizophrenic patients receiving clozapine treatment within the US Department of Veterans Affairs system, using a subset of data obtained from the National Clozapine Coordinating Center. Data were evaluated for 2996 patients (mean age 44.8 ± 10.2 years) treated with clozapine over a 5-year period. Patient psychopathology was evaluated using the Brief Psychiatric Rating Scale (BPRS), and involuntary movements were rated using the Abnormal Involuntary Movement Scale (AIMS). Before clozapine treatment, 42.3% of the patients had a history of suicide attempts, with 5% having attempted suicide during the month before starting clozapine treatment. After treatment only two suicides were observed during the study period (0.1%). Results of the analysis showed a significant improvement (P<0.001) in all of the BPRS subscales and improvement in the AIMS score in these clozapine-treated patients. The authors conclude that treating patients who have a high degree of aggressiveness and suicidality with clozapine may be particularly beneficial.

5. Modaj I, Hirschmann S, Rava A, et al. Sudden death in patients receiving clozapine treatment: a preliminary investigation. J Clin Psychopharmacology 2000;20:325-327.

Using a database from one mental health center in Israel, this retrospective study analyzed the rates of sudden death, suicide, and disease-related death over a period of 6 years and 8 months from 1991-1997 in schizophrenic patients who received clozapine (n= 561) and non-clozapine treatment (n=4918). During this period, there were a total of 10 deaths in the clozapine treated group (1.8%) and 105 deaths in the non-clozapine treated group (2.1%). There were significantly more sudden deaths in the clozapine group (6/561; 1.1%) than in the non-clozapine treated group (14/4918; 0.3%) (P<0.01); however, 2 of the 6 deaths occurred after cessation of clozapine treatment. In contrast, there were significantly fewer disease-related deaths in the clozapine group (2/561; 0.4% vs 86/4918, 1.7%) (P<0.05). The difference in suicide rate was not significantly different between groups (2/561 clozapine-treated patients; 0.36% vs 5/4918; 0.10% in the non-clozapine treated patients). The authors suggest that interpretation of these data should be made with caution in light of the limited number of deaths.

6. Sernyak MJ, Desia R, Stolar M, Rosenheck R. Impact of clozapine on completed suicide. Am J Psychiatry 2001; 158:931-937.

This retrospective study evaluated clozapine's effect on the rate of death due to suicide. Data for this study in the US were obtained from the discharge abstracts of 45,917 Veteran's Administration patients who had psychiatric hospitalizations of at least 1 day during the fiscal years 1992 through 1995, for which the primary discharge diagnosis was schizophrenia. Of these 45,917 patients, 1,415 had received clozapine treatment for the first time while hospitalized during the study period. Of the remaining 44,502 patients, 2,830 were selected as a control group. Propensity scoring was employed to maximize the comparability of the clozapine and control groups. However, patients with any duration of exposure to clozapine were included in the clozapine treatment group without regard to their treatment status at the time of death or their duration of clozapine treatment. Patients who were exposed to clozapine for any length of time had a statistically significant lower overall age-and age-adjusted mortality rate than did those with no clozapine exposure. No data for the exact duration of treatment at the time of death was

provided. There was no significant difference in the rates of suicide between the clozapine-treated (10 suicides/1415 clozapine-treated patients; 0.71%) and nonclozapine-treated patients (23 suicides/2380 non-clozapine-treated patients; 0.97%). This study supports the effect of clozapine on reducing mortality, but does not provide evidence for a reduction in suicidality with clozapine treatment.

NONPOPULATION STUDIES

1. **Meltzer HY and Okayli G. Reduction of suicidality during clozapine treatment of neuroleptic-resistant schizophrenia: impact on risk-benefit assessment. Am J Psychiatry 1995;152:183-190.**

This retrospective mirror-image study at a multi-site, single center in the US compared the suicidality of neuroleptic-resistant and neuroleptic-responsive patients who were diagnosed with chronic schizophrenia or schizoaffective disorder. It further examined whether clozapine treatment decreased suicidality in neuroleptic-resistant patients compared with their pre-clozapine treatment rate. Prior episodes of suicidality were assessed in a total of 183 neuroleptic-resistant and 237 neuroleptic-responsive patients with schizophrenia or schizoaffective disorder. There was no significant difference between these two groups in prior suicidality episodes at baseline. After initiating clozapine treatment during an index hospitalization, suicidality was assessed at weekly intervals during hospitalization and at 6 weeks, 3 and 6 months after hospitalization, and every 6 months thereafter for a mean follow-up period of 3.5 years. The results for suicide were compared with those results obtained from a review of treatment for the 2 years prior to the initiation of clozapine treatment. In the 88 patients who received clozapine for at least 6 months, there was a marked reduction in suicidality compared to the prior history of these same patients. The percentage of patients with suicidality decreased from 47% at baseline to 12% during the follow-up period. There were 22 suicide attempts in the 2 years prior to the initiation of clozapine therapy and only 3 suicide attempts, with low probability for lethality, during the 2 years of follow-up while patients continued to receive clozapine treatment. This represents an 86% decrease in suicide attempts and a concomitant reduction in the lethal potential of the suicide attempts. The results of this study suggest that the use of clozapine reduces suicidality.

2. **Littrell KH, Herth KA, Hinte LE. The experience of hope in adults with schizophrenia. Psychiatric Rehabilitation Journal 1996;19:61-65.**

This prospective longitudinal study assessed the effects of psychosocial treatment and clozapine therapy on the level of hope in patients with refractory schizophrenia and a history of suicide attempts. This study was conducted in 44 adults with schizophrenia at a single center in the US. Its primary focus was on a subgroup of 14 individuals who had made previous suicide attempts. Twelve of the 14 subjects were male. The mean age of the 14 patients was 33 years, and the average dose of clozapine was 550 mg/day. Previous suicide attempts ranged from 1 to 6, with a mean of 2 attempts since diagnosis of disease. The Herth Hope Index (HHI) was used to assess the overall level of hope, the Brief Psychiatric Rating Scale (BPRS) was used to measure psychopathology, and the Social Adjustment Scale-Patient Version (SAS-PT) was used to evaluate reintegration. These measures were administered to the subjects before any psychosocial or clozapine treatment and reassessed monthly, with analyses performed after 6 and 12 months of treatment. Results of the study showed that levels of hope increased significantly

between baseline and after 12 months of treatment ($P<0.001$). None of the participants attempted suicide or were rehospitalized during the 12-month study period. Subjects also displayed an improvement in psychopathology and social functioning. The main findings of this study were improvement in psychopathology, reintegration, and reduction in suicide attempts compared to baseline in adult schizophrenia patients receiving a combination of clozapine and psychosocial therapy and the correlation of these outcomes to levels of hope.

3. Botsis AJ, Giotakos O, Lazaridis P, Petrovas G, Stefanis CN. Clozapine efficacy on suicidal behavior across two main psychiatric disorders.
Eur Neuropsychopharmacol 1997;7(suppl 2):S202.

This prospective study conducted at a single center in Greece examined the effects of clozapine treatment on depression and suicidal behavior in 10 psychiatric inpatients (6 schizophrenics and 4 major depressives with psychotic features). All 10 patients had been treated with high doses of typical neuroleptics (and high doses of antidepressants in the four major depressives) for at least 4 weeks. Clozapine was then administered for 4 weeks (450 mg/day). The patients were evaluated by the BPRS, Modified Overt Aggression Scale, and Montgomery-Asberg Depression Scale during their drug-free period, at the end of treatment with classical neuroleptics, after 4 weeks of clozapine treatment, and again at the end of the third month of their follow-up. The patient's clinical symptoms showed improvement after 10 days of clozapine treatment, and their suicidal behaviour and general psychopathology were diminished after 3 weeks of clozapine treatment. The authors concluded that clozapine may be efficacious in reducing suicidality.

4. Spivak B, Roitman S, Vered Y, et al. Diminished suicidal and aggressive behavior, high plasma norepinephrine levels, and serum triglyceride levels in chronic neuroleptic-resistant schizophrenic patients maintained on clozapine.
Clin Neuropharmacol 1998;21:245-250.

This retrospective, mirror-image study conducted at a single center in Israel evaluated the effects of clozapine on impulsiveness and aggression (including suicidality) and prospectively examined its effect on serum lipids, serotonin (5-HT), and norepinephine (NE) levels. The patient population consisted of 30 neuroleptic-resistant chronic schizophrenic patients (19 men and 11 women) who were maintained on clozapine (mean dose ± SD of 295.0 ± 165.3 mg/day) for 1 year and a control group of 20 chronic schizophrenic patients (10 men and 10 women) who were maintained on typical antipsychotic agents for 1 year. Aggressiveness and impulsiveness was assessed by the Overt Aggression Scale (OAS) and Impulsivity Scale (IS). In addition, a retrospective evaluation of aggressive behavior during the period preceding the last year of antipsychotic treatment (time point when patients in both groups had been maintained on typical antipsychotics) was performed. Suicidal attempts or suicidal behavior during the year preceding clozapine or typical antipsychotic treatments were categorized as present or absent. The results of the study showed that the clozapine-treated patients had significantly less impulsiveness (IS score) and aggressiveness (OAS score) than the control group ($P<0.05$). None of the clozapine-treated patients had attempted suicide during the 1 year of clozapine treatment compared with 5 patients in the control group (Fisher's exact test, $P<0.05$). Results of the laboratory test analyses showed that the clozapine group had significantly higher triglyceride levels and platelet-poor plasma concentrations of norepinephrine than the control group. Platelet-poor plasma 5-HT

levels were similar in both groups, as were cholesterol and LDL levels. The major finding of this study was the demonstration of lower levels of suicidality, impulsiveness, and aggressiveness in chronic schizophrenic patients maintained on clozapine for 1 year compared with patients treated for the same period with typical antipsychotics.

5. Ciapparelli A, Dell'Osso L, Pini S, Chiavacci MC, Fenzi M, Cassano GB. Clozapine for treatment-refractory schizophrenia, schizoaffective disorder, and psychotic bipolar disorder: a 24-month naturalistic study. J Clin Psychiatry 2000;61:329-334.

This prospective study conducted in Italy evaluated the response to clozapine over a 24-month period in patients who had schizophrenia, schizoaffective disorder, or psychotic bipolar disorder. This study was conducted in 91 adult psychotics: 31 schizophrenics, 26 with schizoaffective disorders, and 34 with psychotic bipolar disorder. Sixty-three of the 91 patients were male. The mean age of the three groups ranged from 32.2 to 36.5 years. The mean dose of clozapine at endpoint was 236, 237 and 160 mg/day for the schizophrenic, schizoaffective, and psychotic bipolar patients, respectively. At baseline, 26 of the 91 patients had made a suicide attempt or had had suicidal ideation. Patients were treated with clozapine for 24 months in combination with other neuroleptics and other medications as appropriate (i.e., anticonvulsants, antidepressants, lithium, etc.). The severity of psychopathology was assessed using the BPRS-Expanded version (BPRS-E) at baseline, and after 1, 6, 12, and 24 months of clozapine treatment. Patients were also evaluated at baseline and after 12 and 24 months using the CGI-Severity of Illness Scale (CGI-S). Suicidal ideation was also assessed at baseline by the interviewer on the basis of clinical judgment. The presence of suicidal ideation at baseline correlated with a lower BPRS total score after 24 months. When the analyses were restricted to patients with suicidal ideation at baseline, a significant reduction in the BPRS-E suicide item score was found at 24 months $P<0.27$). There was a significant and persistent clinical improvement (reduction in BPRS total scores and CGI-S scores) in all patients at 24 months with clozapine treatment. Improvement was significantly greater among patients with schizoaffective disorder and bipolar disorder than those with schizophrenia. The authors concluded that the results of this study showed clozapine to be effective in reducing suicidality after 24 months of treatment in patients with suicidal ideation and gave further support for the use of clozapine for lowering suicide risk in patients with schizophrenia and in those with severe mood disorders.

CASE REPORTS/OBSERVATIONAL DATA

Four case reports were identified from the literature. Three of these 4 patients were female. Subject age was provided for three of the cases and ranged from 34 to 44 years old. Two of the patients were schizophrenic and 2 had bipolar disorders. Remission or reduction of suicideal ideation or suicide attempts was observed in 3 of the 4 cases after treatment with Clozaril. Clozaril treatment duration in two of these cases was 12 months (325 mg/day) and 3.5 weeks (125 mg/day). (VangalaVR, Brown ES, Suppes T. Clozapine associated with decreased suicidality in bipolar disorder: a case report. Bipolar Disorders 1999;2:123-124.; Privitera MR, Lamberti JS, Maharaj K. Clozapine in a bipolar depressed patient. Am J Psychiatry 1993;150:986.) For the third case, only the daily dose was provided (450 mg). (Martin, LM, Pablos EG, Andres RMS. Reduccion del riesgo de suicidio en una paciente esquizofrenica tratada con clozapina. An Psiquiatria [Madrid] 1997;13:390-391.) In the fourth case report, the patient

received 400 mg of Clozaril/day for 6 weeks, at which point the patient committed suicide. (Tamam L, Ozpoyraz N. Suicide during clozapine treatment: a case report. Isr J Psychiatry Relat Sci 2001;38:127-132.) This patient had no history of suicidal ideation and had shown improvement in clinical symptoms after initiating Clozaril treatment.

Two additional observational retrospective reports from Canada and Italy were identified from the literature. In the Canadian report, no suicides were observed in continuous users (n=11 patients) of Clozaril (3-year treatment duration), and 2 suicides were observed in 11 patients who had taken Clozaril for 1 and 9 days, respectively, and discontinued therapy; therefore, these were considered unrelated to Clozaril. (Dickson RA, Dalby JT, Williams R, Warden SJ, et al. Hospital days in clozapine-treated patients. Can J Psychiatry 1998;43, 945-948.) In the Italian report, a reduction in suicidality with Clozaril treatment was reported: 2 suicides vs 22 in the total population of 103 patients examined. (Altamura AC, Bignotti S, Tura GB, et al. Suicidal behaviour in schizophrenia: a retrospective study. European Neuropsychopharmacol 1999;9(Suppl. 5):S271.) The authors concluded that clozapine has a possible role in reducing suicide or suicidal ideation.

REVIEW PAPERS

A literature search identified 17 papers that reviewed previously published data on suicidality and clozapine. Reprints of these papers were obtained and reviewed and found to contain no data or references that have not been presented above.

CONCLUSION

Between 1991 and 2001, reports of 11 studies of the effects of clozapine on suicidality in patients with schizophrenia or schizoaffective disorder were identified. Of theses, 6 were population studies and 5 were non-population studies. In addition, 4 case study reports and 2 observational reports were identified. Eight studies used retrospective analyses with a total clozapine-treated patient population of 86,327, and 3 were prospective studies with a total clozapine-treated population of 145 patients. None of the studies were double-blind comparisons of two or more treatments. Across all studies, the majority of patients were between the ages of 18 and 60. Where the published literature described the clozapine dosage received by these patients, the mean dosage by study ranged from 236 mg/day to 550 mg/day. This is in accord with standard medical practice for the treatment of schizophrenia. Analysis of these data from 11 geographically diverse locations, as well as the anecdotal evidence from 4 individual case reports and 2 observational reports provide strong evidence supporting the efficacy of clozapine in reducing suicidality and suicide in patients with schizophrenia and schizoaffective disorder.

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Littrell KH, Herth KA, Hinte LE. The experience of hope in adults with schizophrenia. Psychiatric Rehabilitation Journal 1996;19:61-65.

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REVIEW PAPERS

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Table 1. Clozaril® Publications Summary

Author/Year	Sample Size (n)	Design	Population Characteristics	Clozapine: Treatment duration	Clozapine: Dose/day	Reference Group/Time	Suicide Rate/Effect on Suicidality
POPULATION STUDIES							
Walker 1997	Clozapine-treated: 67,072	US; retrospective analysis of patients treated 1991-1993; examined mortality rates	Patients enrolled in US Clozaril National Registry from 1991 to 1993. Population analyzed by age groups of 10-54 and 55-94 years	Range of mean observed days/subject **Current**: 47-339 **Recent**: 7-43 **Past:** 99-114	Not provided	Recent and past clozapine users compared to current users	Suicides: 24 current/18 recent/33 past users; suicides/100,000 person-yrs=39/246/222. Suicide rate ratio = 0.17 for current clozapine users compared w/ past users.
Reid 1998	Total: 30,130 Clozapine-treated: 1310	US (Texas state psychiatric facilities); retrospective analysis	Schizophrenic/schizo-affective pts; examined annual suicide rates for 2 years (1993-95) of 30,130 pts. Subgroup of 1,367 clozapine treated pts evaluated over 6-yr period (1991-96) .	At least 30 days exposure	No mean dose provided	30,130 schizophrenic/ schizoaffective patients	Suicides: 1/1310 cloz-trt; 38/30,130 total pop; 5-fold decrease in suicide rate in cloz-treated patients
Munro 1999	Clozapine-treated: 12,760	UK and Ireland; retrospective analysis of clozapine-treated (1990-1998); Aim: quantification of risk factors for agranulocytosis	Treatment-resistant schizophrenic patients	1 day – 7.6 years	Mean dose 388 mg/day (mean max dose 462 mg/day)	NA	13/12,188 clozapine treated patients; decreased suicide risk compared with rate in schizophrenic patients in UK

Author/Year	Sample Size (n)	Design	Population Characteristics	Clozapine: Treatment duration	Clozapine: Dose/day	Reference Group/Time	Suicide Rate/Effect on Suicidality
Sajatovic 2000	Clozapine: 2996	US; VA database, 5-y period, retrospective study; compared endpoint to baseline BPRS and AIMS scores	Schizophrenic cloz-trt patients in US VA system; mean age: 44.8 years	Not provided	Not provided	NA	Suicide rate 0.1% after clozapine treatment (2 suicides); sig. Decrease compared with before trt; Sig. improvement on BPRS
Modaj 2000	Clozapine: 561; non-clozapine-: 4918	Israel; retrospective analysis 1991-1997; database of one mental health center	Schizophrenic patients in one mental health center	Not provided	Not provided	Non-clozapine treated (other agents)	2/561 clozapine-treated; 5/4918 non-clozapine treated; No sig difference in suicide rate between the two groups
Sernyak 2001	Total sample: 45,917; Clozapine-treated: 1415; noncloz-treated: 2380	US; VA database; retrospective analysis: 1992-1995; examined overall mortality and cause-specific mortality	Schizophrenic patients: mean age: cloz trt=43.0 yr, noncloz trt=43.6yr	28% received clozapine <1 year, 72% receivedclozapine ≥1 year	Not provided	Without record of any clozapine treatment	Suicides: long-term cloz=5/1018; short-term cloz=5/397; non-cloz trt: 23/2,380; No sig. differences in suicide rate between clozapine trt and non-clozapine trt pts;
NONPOPULATION STUDIES							
Meltzer 1995 and 1998[1]	Total pop: 420; neuroleptic-resist. cloz trt: 183; cloz-trt ≥ 6 months: 88	US; 1986-1993; mirror-image, retrospective. Examined suicidality	schizophrenic or schizoaffective patients;	2-year duration of clozapine treatment	Mean dose: 500 mg/day	Neuroleptic – responsive patients; pre- vs post- trt of neuroleptic resistant patients	3/88; Sig. Decreased suicidality by 86.4% in clozapine-trt patients compared w/ before clozapine treatment

Author/Year	Sample Size (n)	Design	Population Characteristics	Clozapine: Treatment duration	Clozapine: Dose/day	Reference Group/Time	Suicide Rate/Effect on Suicidality
Littrell 1996	Total clozapine-treated: 44; subset with previous suicide attempts: 14	US; prospective, open–label study; examined levels of hope (HHI) suicide attempts, BPRS, and reintegration (SAS-Pt)	Schizophrenic patients	12 months	Mean dose: 550 mg/day	Compared rating scale results after 6 and 12 months of clozapine treatment with baseline scores	Reduced suicide attempts to 0 during a 12-month study period, increased hope levels; improved general clinical psychopathology and reintegration
Botsis 1997	10 clozapine-treated	Greece; prospective, open label. Examined suicidal behavior and psychopathology	Schizophrenics and major depressive in-patients	4 weeks	Daily dose of up to 450 mg/day	Treatment period w/ std neuroleptics before clozapine treatment	Reduced suicidal behavior and general clinical psychopathology
Spivak 1998	30 clozapine-treated; 30 std antipsy-chotics	Israel; retrospective mirror-image analysis of impulsive/aggressive behavior and suicidality	Neuroleptic-resistant schizophrenic patients clozapine treatment for 1 year; mean age 36.9 year	1 year	Mean dose of 295 mg/day	Chronic schizophrenics w/1 year treatment w/classical antipsychotics	Suicides: 0/30 clozapine trt; 5/30 control group; sig. decreased suicide rate in clozapine treated patients.
Ciapparelli 2000	91 trt-resistant psychotics: 31 schizo-phrenic; 26 schizo-affective; 34 bipolar	Italy; prospective, open-label study; comparison of clozapine treatment in the three types of psychotics	Treatment-resistant psychotic patients; range in mean age 32.2-36.5 year for three groups	24 months	236, 237, and 160 mg/d for schizo-phrenic, schizo-affective, bipolar pts, respectively	Comparison of clozapine treatment in the three types of patients	Inpatients with suicidal ideation at baseline, there was a significant reduction in the BPRS-E suicide item score at 24 months of clozapine treatment.

Author/Year	Sample Size (n)	Design	Population Characteristics	Clozapine: Treatment duration	Clozapine: Dose/day	Reference Group/Time	Suicide Rate/Effect on Suicidality
CASE REPORTS/OBSERVATIONAL DATA							
Privitera 1993	1	US	44-yr-old bipolar female	3.5 weeks	125 mg	NA	Substantial decrease
Martin 1997	1	Spain	17-yr-old female		450 mg	NA	Substantial decrease
Dickson 1998	26	Canadian; retrospective review	Treatment-resistant schizophrenic patients; Groups: clozapine continuous use (11 pts), interrupted use (4 pts), discontinued (11 pts); mean age: 31.8 year	Continuous users: 3 years	Not provided	Three groups compared with each other	2 suicides in group of 11 discontinued; occurred after discontinuing treatment, treatment durations of 1 and 9 days (not considered clozapine-related)
Altamura 1999	103	Italian, retrospective review	Schizophrenic/ schizoaffective patients; 68 males and 35 females	Not provided	Not provided	NA	Suicides: 2 with clozapine-trt (no denominator provided); 22 suicides in total pop of 103; cloz associated with reduction in suicidality
Vangala 1999	1	US	34-yr-old female	12 months	325 mg	NA	Substantial decrease
Tamam 2001	1	Turkey	36-yr-old male	6 weeks	400 mg	NA	Suicide death
REVIEW PAPERS							
A literature search identified 17 Review Papers that were obtained and reviewed. No additional pertinent references to Clozaril and suicide were observed other than the ones summarized above in this Table.							

[1] The Meltzer 1998 publication only discusses the 88-patient clozapine-treated cohort whose data were presented in the Meltzer 1995 publication.